REMARKS

Reconsideration of this application is requested. Claims 1-21 are in the application subsequent to entry of this amendment.

The claims have been amended in order to more particularly point out and distinctly claim that which applicants regard as their invention. More specifically, claim 1 has been amended in order to attend to the examiner's concerns stated in item 2 of the Official Action.

The formulations of the present invention as described in the paragraph bridging pages 6 and7 of the specification are designed to be diluted with water (see page 7, lines 26-28) and as such are essentially non-aqueous. See also the illustrative formulations of Examples 1-6 none of which contain water, thus it is appropriate to characterize them as non-aqueous. Claims 1, 2, 8 and 9 are also amended to employ "consisting essentially of" terminology as used in claim 12.

Apart from the formalities issue, now resolved as explained above, the Official Action consists of four separate prior art-based rejections. Before addressing these rejections, however, it is useful to again review the essential aspects of the present application.

Applicants describe novel pharmaceutical dosage forms for anticancer drugs, and paclitaxel in particular, in which the active drug is formulated as storage stable self-emulsifying preconcentrate. The composition is defined as a pharmaceutical composition comprising an anticancer drug as active ingredient dissolved in a carrier system three type of components, (1) at least one hydrophobic component, (2) a

hydrophilic component and (3) at least one surfactant. The hydrophobic component is selected from triglycerides, diglycerides, monoglycerides, free fatty acids, and fatty acid esters, individually or in combination. The hydrophilic component is a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol.

Applicants have found that particularly stable anticancer drug formulations especially the taxanes, that self emulsify in aqueous medium giving an average particle size in a range of about 10 nm to about 10 microns. Improved bioavailability characteristics result. Also described are self-emulsifying preconcentrates that disperse, without the input of high energy (i.e., other than gentle mixing to cause dispersion), to form droplets of average size of up to about 10 microns.

The specific points raised in the outstanding Official Action are now addressed in the order present:

4. Kaufman ('247) discloses a composition and method of making an oil-in-water "emulsion" containing taxane. The composition claimed in Kaufman is "...a taxane; an oil; water; and a surfactant..." (page 20, lines 4-7). The process for preparing the oil-in water emulsion in which the taxane is dissolved in the dispersed oil phase involves dissolving the taxane in oil containing a co-solvent (ethanol). The co-solvent is then removed by evaporation ("the alcohol was removed") leaving a solution of the taxane dissolved in the oil. The oil is then dispersed in the water phase in the presence of a surfactant using standard homogenization techniques (see Abstract & page 10, lines 1-23 and page 11, lines 1-2). The techniques used by Kaufman to form the emulsion are very high energy processes and contrast with the gentle mixing required to cause dispersion in

the applicants' invention. The final composition does not contain ethanol as stated by the examiner. On the other hand, applicants' compositions contain a hydrophilic component, such as an ethanol, but not water.

5. The publication of Lundberg et al also discloses a composition and method of making oil-in-water emulsion in which the taxane (paclitaxel) is dissolved in the oil phase. The compositions and methods of manufacture disclosed in both Kaufman and Lundberg are very similar. Both Kaufman and Lundberg use phospholipid as a primary surfactant to make oil-in-water "emulsions" and optionally a second on-ionic or ionic surfactant to further stabilize the emulsion and both compositions contain water. In both cases, a high energy equipment is used to form the stable oil-in-water emulsion; sonicator in the case of Lundberg (page 17, "preparation of drug emulsions") and homogenizer in the case of Kaufman (page 10, lines 19-23). On the other hand, the present application discloses compositions that contain no water. Further, when the preconcentrate described in the present application is added to water it immediately disperses to form an optically clear mixture.

7. Sime et al disclose a sesquiterpene component of grapefruit juice as an inhibitor of oxidative enzymes and its use. As discussed above, the compositions described in Kaufman and Lundberg are fundamentally different to Parikh. Therefore, we maintain Parikh is not obvious from Sime in light of Kaufman or Lundberg.

8. The rejection advanced in this section appears to be based on a fundamental misunderstanding. Microemulsions and emulsions are fundamentally different. A microemulsion is "a system of water, oil and amphiphile which is a single

optically...(i.e., transparent)...isotropic and thermodynamically stable liquid solution" (marked section page 32 Attwood see Attachment 1-- see also the discussion at page 2, last paragraph, of the specification. On the other hand, emulsions are inherently unstable and require mechanical work in order for their formation (marked section page 32 Attwood see Attachment 1). Emulsions cannot be converted to microemulsions by the addition of "greater amounts of surfactants" as suggested by the examiner. As stated above, both Kaufman and Lundberg disclose standard oil-in water emulsions and not self-emulsifying solution preconcentrates as described in the present application. It is apparent to one skilled in the art that by simply increasing the amount of surfactants, one cannot convert an oil-in-water emulsion into a self-emulsifying preconcentrate system.

9. Similar to #8 this comment deals with Kaufman in view of Charman ('987) and Lundberg in view of Kaufman. As stated above, here again it is apparent to one skilled in the art that simply by increasing the amount of surfactants one cannot convert either Kaufman or Lundberg's oil-in-water emulsion into a self-emulsifying preconcentrate as defined by applicants' claims.

Reconsideration and favorable action are solicited.

Respectfully submitted,

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